Risk of Cancer in Children With AIDS

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Context Population-based data on cancers associated with acquired immunodeficiency syndrome (AIDS) in children are lacking.

Objective To determine risk of pediatric AIDS-associated cancers.

Design, Setting, and Participants Using records from 11 locations in the United States for varying periods between 1978 and 1996, we linked data for children aged 14 years and younger at AIDS diagnosis to local cancer registry data.

Main Outcome Measures Cancer frequency and, in the 2-year post–AIDS onset period, cancer incidence and relative risk (RR; measured as standardized incidence ratio), by cancer type.

Results Among 4954 children with AIDS, 124 (2.5%) were identified as having cancer before, at, or after AIDS onset, including 100 cases of non-Hodgkin lymphoma (NHL), 8 of Kaposi sarcoma (KS), 4 of leiomyosarcoma, and 2 of Hodgkin disease; there were 10 other or unspecified cancers. Expected numbers for all cancers identified in the study sample, based on population rates (using area-specific registry data), were less than 1. In the first 2 years after AIDS diagnosis (5485 person-years), NHL incidence was 510 per 100000 person-years (RR, 651; 95% confidence interval [CI], 432-941). Median time for developing NHL after AIDS diagnosis was 14 months (range, 3-107 months). The most common type of NHL was Burkitt lymphoma. However, the risk of primary brain lymphoma (91 per 100000 person-years) was especially high (RR, 7143; 95% CI, 2321-16692), and 4 cases were diagnosed more than 2 years (range, 37-98 months) after AIDS onset. Leiomyosarcomas also tended to occur several years after AIDS onset, with 3 of the 4 cases occurring 33 to 76 months after AIDS diagnosis, whereas KS was reported only at or within 2 years of AIDS diagnosis. Hodgkin disease risk was also significantly increased (RR, 62; 95% CI, 2-342).

Conclusions The spectrum of AIDS-associated pediatric cancers resembled that seen in adults, with the addition of leiomyosarcoma. Both primary brain lymphomas and leiomyosarcomas tended to occur in children surviving several years after AIDS onset. Because the expected numbers of these cancers in this population were less than 1 and because of the small numbers of some types of observed cancers, the RR estimates are imprecise and caution is warranted in their interpretation.

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CANCERS ARE WELL KNOWN TO occur in excess in persons with acquired immunodeficiency syndrome (AIDS). These tumors include, prominently, Kaposi sarcoma (KS), a cancer occurring especially in homosexual men with AIDS, and non-Hodgkin lymphoma (NHL), which has similar incidence in all groups regardless of the route of exposure to human immunodeficiency virus (HIV).[1] In adults, invasive cervical cancer is considered an AIDS-defining disease, and other cancers such as Hodgkin disease, anal cancer, and testicular cancer have been linked to AIDS.[2] Children with AIDS are at lower risk of cancer than are adults, and they constitute only a small fraction of persons with AIDS. Thus, studies of cancer in children have mainly involved case series.[3-5] We sought to provide a population-based overview of the spectrum of malignancies in children with AIDS.

METHODS

We linked cancer registry data to 366034 cases of AIDS in 11 areas. These areas were included because they had a relatively high AIDS incidence and cancer registry coverage of the same population. We evaluated only data obtained during the periods when both registry bases were considered complete, which varied by registry: the states of New York (January 1981–December 1994), Massachusetts (January 1982–December 1995), Connecticut (November 1980–September 1995), New Jersey (January 1979–December 1996), Florida (January 1981–December 1995), and Illinois (January 1980–December 1995); and the urban areas of Seattle, Wash (January 1983–June 1996), San Francisco, Calif (January 1980–September 1995), Los Angeles, Calif (March 1978–February 1996), Atlanta, Ga (May 1980–December 1994), and San Diego, Calif (January 1988–December 1995). Most data were from an era before highly active antiretroviral therapies became widely used. Between 1988 and 1990, AIDS–cancer linkages in 50050 persons in New Jersey, California, Florida,

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and Atlanta, Ga, were evaluated using similar methods,[2,6,7] but there were too few children to analyze pediatric cancer risk.

To perform linkage, we used AutoMatch, versions 3.0 and 4.1 (MatchWare Technologies, Inc, Burtonsville, Md), which weighted the likelihood of subject matching on the basis of identical or near-identical information. By order of priority, we included, when available, social security number, last name, first name, middle name or initial; the soundex codes for the last name, first name, and middle name or initial; birth and death dates; race; sex; and home address. Further details of the matching procedures, confidentiality protection, and analysis approaches are provided elsewhere.[2,6,7]

Expected numbers of cancers were computed from data in the geographic areas where the AIDS cases occurred, except for Illinois, where rates from National Cancer Institute Surveillance, Epidemiology, and End Results Registries in Iowa and Detroit were substituted because we did not have histology-specific information. Coding was based on the *International Classification of Diseases for Oncology, Second Edition*.[8] The KS analyses excluded data from Florida because of concern about diagnostic accuracy. While AIDS registries identified Hispanics, cancer registries did not have data specific to this group. Therefore, expected cancers for Hispanics were based on rates for whites, on the assumption that most Hispanics would be classified as white in cancer registry data. Cancer reports were accepted from either AIDS or cancer registry data. When in conflict, cancer registry information about histology was preferentially accepted as likely to be more accurate. However, after noting a significant dearth of information about NHL sites in the cancer registry data, we accepted the NHL localization as primary brain lymphoma from either the AIDS or the cancer registry.

Children were followed up from birth or up to 5 years before their AIDS diagnosis to the date of death or last complete cancer registry information, whichever came first. Nine children had AIDS-defining cancer diagnoses (8 NHL, 1 KS) recorded in the cancer registry before AIDS was diagnosed (median, 6.5 months; range, 1-14 months). Following standardized procedures,[2,6,7] the date of AIDS onset was moved back to that date, since these were within 5 years of another AIDS diagnosis. Screening of donated blood for HIV antibodies became routine in early 1985. To avoid linkages occurring because children became HIV infected via transfusions related to their cancer, we excluded all tumors occurring prior to 1985 unless the tumor occurred at or after another AIDS diagnosis.

The AIDS onset period was defined as 6 months before to 3 months after the precise date given to the AIDS diagnosis to accommodate slight variations in timing of receipt of cancer reports by the AIDS or cancer registries. Cancer incidence could not be evaluated during the AIDS period because most of the observed cancers (58 cases of NHL and 4 cases of KS) were AIDS-defining. The appropriate denominator for cancer incidence data in this group would be HIV-infected children, but we did not have such data. However, children with AIDS are, by definition, HIV-infected, and therefore we could use the population of children without the specific cancer under study who were followed into the post-AIDS onset period as the population at risk of developing that cancer.

Cancer incidence rates per 100 000 person-years were therefore calculated for a 2-year period after AIDS diagnosis (defined as 4 through 27 months after AIDS onset). Expected cancers were calculated as the sum of the products of population incidence and person-time in the strata of age (≤4, 5-9, and 10-14 years), sex, and race (whites, blacks, Hispanics, and other or unknown). Relative risk (RR) calculations (RRs were measured as standardized incidence ratios) were based on dividing the observed by the expected number of cancer cases for the 2 years after AIDS onset, and 95% confidence intervals (CIs) were calculated based on the Poisson assumption.[9] Because cases of cancer in children with AIDS contribute to the contemporaneous background rates, RRs are conservative. Comparisons of frequencies were made by χ^2 methods and Fisher exact (2-tailed) tests. Descriptive statistics are reported as mean (SD).

RESULTS

Overall, 4954 children aged 14 years and younger at AIDS diagnosis were identified in the linkage areas during times when both AIDS and cancer registries were complete. New York contributed the largest number of cases (39.8%), followed by Florida (24.1%), and New Jersey (14.6%). By sex, 51.2% were boys; and by race, 60.6% were black, 23.5% were Hispanic, 15.1% were white, and 0.8% were of other or unknown race. The mean (SD) age at AIDS onset was 2.7 (3.6) years, but 36.9% of children were in the first 12 months of life, and a further 18.6% were 13 to 24 months old, so that the median age was 1 year (interquartile range: 1-4 years). Transmission was predominately via exposure to an infected mother (90.4%) or contaminated blood or blood products (7.3%). The latter category includes children with hemophilia.

Among these children, 124 (2.5%) were identified as having cancer either pre-AIDS, at AIDS onset, or post-AIDS. By type, there were 100 cases of NHL (81%), 8 of KS (6%), 4 of leiomyosarcoma (3%), and 2 of Hodgkin disease (2%); there were 10 other or unspecified types (8%) (TABLE 1). One child may have had 2 cancers, ie, immunoblastic lymphoma (IBL) followed 4 years later by Burkitt lymphoma (BL). Only the first cancer is further considered. Cancer was more frequent in boys (2.9%) than girls (2.0%) ($P=.04$). By race, cancer was less frequent in blacks (1.9%) than in whites (3.1%; $P=.06$) and Hispanics (3.4%; $P=.01$). The mean (SD) age at AIDS diagnosis for children who developed cancer was 3.6 (3.7) years (median, 2 years), and the mean (SD) age at which they developed cancer was 4.5 (3.7) years (median, 3 years). Cancer risk was not significantly related to

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HIV-exposure category after adjusting for age and sex.

The distribution of cancers by time from AIDS onset is given in Table 1. During the 2 years after AIDS diagnosis, 5485 person-years of observation were accrued for 3753 children (mean, 17.5 months). During this period, 36 cancers occurred vs 0.89 expected (RR, 40; 95% CI, 28-56). The cancer incidence was 656 per 100 000 person-years in this period (TABLE 2). Incidence was higher in boys than girls, and this pattern was also seen in the general population.

Non-Hodgkin Lymphoma

Among the 100 cases of NHL, 34 were BL, including Burkitt-like lymphomas, 19 were IBL, 23 were primary brain lymphomas (without regard to histology), and 24 were unspecified NHL. Only 35% were recorded in both AIDS and cancer registries, whereas 37% were only in the AIDS registry data and 28% were only in the cancer registry data. Brain sites were often (61%) reported only in the AIDS registry data, which did not provide histology information for brain lymphoma.

The cases of NHL occurred in a broad range of ages, from younger than 1 year to age 13 years, but the average age at AIDS diagnosis was 3 to 3.5 years for all histologic subtypes. Most cases of NHL (n=58) were concurrent with AIDS onset (Table 1). The median time for developing NHL after AIDS was 14 months (range, 3-107 months). However, the late occurrence of 4 cases of primary brain lymphoma (37, 38, 40, and 98 months after AIDS onset) represented a notably longer time to onset than for other specified NHL subtypes. In the 2 years following AIDS diagnosis, the NHL incidence was 510 per 100 000 person-years and the RR was 651 (95% CI, 432-941) (Table 2). Regarding histology, BL was the most common type.

Overall, NHL incidence rose as the age at AIDS diagnosis increased (unpublished data from study). The incidence in boys was higher than in girls (660 vs 345 per 100 000 person-years), but because background incidence rates for NHL are higher in boys, RRs were similar (604; 95% CI, 359-957; and 675; 95% CI, 309-1282, respectively). The incidence in blacks (450 per 100 000 person-years) was slightly lower than either whites (480) or Hispanics (551), a pattern also generally seen in each NHL subtype (unpublished data from study). Because the background incidence rate for primary brain lymphoma was lower than for BL or IBL, the RR of primary brain lymphoma (7143; 95% CI, 2321-16 692) was much higher than for BL (656; 95% CI, 292-1245) and IBL (815; 95% CI, 297-1774).

Table 1. Cancer Diagnoses by Tumor Type, Relative to AIDS Onset*

	Months						
	Pre-AIDS		AIDS	Post-AIDS			
	−60 to −25	−24 to −7	−6 to 3	4 to 27	28 to 60	>60	Total
Non-Hodgkin lymphoma	0	0	58	28	10	4	**100**
Burkitt	0	0	23	9	1	1	**34**
Immunoblastic	0	0	12	6	1	0	**19**
Primary brain	0	0	14	5	3	1	**23**
Other, unspecified	0	0	9	8	5	2	**24**
Kaposi sarcoma	0	0	4	4	0	0	**8**
Hodgkin disease	0	0	1	1	0	0	**2**
Leiomyosarcoma	0	0	1	0	2	1	**4**
Other/unknown	1	1	1	3	3	1	**10**
Total, All Sites	**1**	**1**	**65**	**36**	**15**	**6**	**124**

*AIDS indicates acquired immunodeficiency syndrome. Values for pre-AIDS cancers were included indicating that the cancer was not AIDS-defining (ie, not non-Hodgkin lymphoma or Kaposi sarcoma). The rationale for analysis of pre-AIDS cancers was to determine if pre-AIDS to post-AIDS risks increased as might be expected if the cancer was related to the advancing immunosuppression. However, too few children had cancer onset prior to AIDS to provide robust trends.

Table 2. Observed and Expected Cancers, and Incidence and Relative Risk by Type, After AIDS Onset*

	Observed	Expected	Incidence in Children With AIDS†	Relative Risk (95% CI)
All cancers	36	0.89	656	40 (28-56)
Boys	24	0.50	883	48 (31-71)
Girls	12	0.40	460	30 (16-53)
Whites	6	0.16	720	39 (14-84)
Blacks	18	0.49	539	37 (22-59)
Hispanics	11	0.24	866	46 (23-82)
Other/unknown race	1	0.01	433	94 (2-521)
Non-Hodgkin lymphoma	28	0.04	510	651 (432-941)
Burkitt	9	0.01	164	656 (292-1245)
Immunoblastic	6	0.01	109	815 (297-1774)
Primary brain	5	<0.01	91	7143 (2321-16 692)
Other/unknown	8	0.02	146	376 (162-741)
Kaposi sarcoma‡	4	0.01	97	NE
Hodgkin disease	1	0.02	18	62 (2-342)
Leiomyosarcoma§	0	<0.01	. . .	NE
Other/unknown sites	3	0.83	55	4 (1-11)

*AIDS indicates acquired immunodeficiency syndrome; CI, confidence interval; and NE, not estimated. Children are aged 14 years and younger. Incidence is measured in the 2 years (defined as 4-27 months) after AIDS onset.
†Because the expected numbers of these cancers in this population were less than 1 and because of the small numbers of some types of cancers, the relative risk estimates are imprecise and caution is warranted in their interpretation. Incidence is measured per 100 000 person years.
‡Excludes data from Florida. The relative risk was NE because all background cases were AIDS-related.
§In the 2 to 5 years after AIDS diagnosis, the relative risk was 1915 (232-6915), based on 2 cases. Because the cases occurred after the 2-year interval following AIDS onset, no incidence values are included for leiomyosarcoma, as indicated by ellipses.

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Kaposi Sarcoma

Eight children were diagnosed with KS. Four cases were identified at the time of AIDS diagnosis, and 4 occurred 5 to 15 months after AIDS onset. In these subjects, the average age at AIDS onset and KS diagnosis were 5.6 years and 6.0 years, respectively. Five children with KS were boys. Route of HIV exposure was mother-to-child in 6 cases and via blood or blood products in 2 cases. In 1 instance, the mother was known to have been exposed to HIV by a bisexual partner ($P = .09$ for risk association).

The incidence of KS in the 2 years after AIDS onset was 97 per 100 000 person-years, being higher in boys (136) than in girls (52) and higher in whites (150) than in blacks (89) or Hispanics (86). Incidence rates (per 100 000 person-years) were lowest in young children with AIDS, being 33 in those younger than 5 years, 284 in 5- to 9-year-olds, and 260 in 10- to 14-year-olds. The RR was not calculated because all KS reports involved children with AIDS.

Hodgkin Disease

Two children with AIDS, both Hispanic boys aged 4 and 9 years, were diagnosed with Hodgkin disease. The incidence (based on 1 case) was 18 per 100 000 person-years in the 2 years after AIDS diagnosis, and the RR was 62 (95% CI, 2-342) (Table 2).

Leiomyosarcoma

One boy and 3 girls were diagnosed as having leiomyosarcoma. Three were blacks and 1 was of other or unknown race. At AIDS diagnosis, they were in the first year of life, and aged 1, 1, and 6 years, and at cancer diagnosis they were in the first year of life, and aged 4, 7, and 9 years, respectively. Three children had a notably long period between AIDS and cancer: 33, 33, and 76 months. No case fell within the 2 years after AIDS diagnosis used to assess the incidence and RR. However, finding 3 cases more than 2 years after AIDS onset, when a relatively lower proportion would have still been in follow-up, implies a very high late risk. Based on 2 cases occurring from 2 to 5 years after AIDS onset, the RR for this time period was 1915 (95% CI; 232-6915).

Other Cancers

We identified 10 children with other or unspecified cancers in cancer registry data. Three cancers occurred in the 2 years after AIDS onset (RR, 4; 95% CI, 1-11). One cancer was a mediastinal ganglioneuroblastoma diagnosed in 1990, 45 months before AIDS onset. The others were diagnosed as malignant histiocytosis, fibrous histiocytoma, and neurofibrosarcoma (3, 4, and 41 months after AIDS onset, respectively). One cancer was a fusiform or spindle cell tumor of the liver (diagnosed 40 months after AIDS onset). Five were unspecified cancers. One, an ill-defined connective tissue tumor of the limb, occurred 7 months before AIDS onset; 3 tumors (with origins in oral cavity, brain, and lymph node) occurred in the 2 years after AIDS onset; and 1 (origin in lung) occurred 70 months after AIDS onset.

One case of leukemia was observed, but histologically, the cells were Burkitt-like, and the case was assigned to the BL group. Two other cases of leukemia occurred in the period before 1985, both several years before AIDS onset. Those cases were excluded because the HIV infection might have been caused by blood products given as part of clinical care for the leukemia. No other case of leukemia was seen, but only 0.7 cases were expected among children with AIDS in the entire time span from 5 years before to 5 years after AIDS diagnosis.

COMMENT

In this study we assessed cancer risk in 4954 children with AIDS, which is approximately 70% of the 6948 children (younger than 14 years) reported as having AIDS to the Centers for Disease Control and Prevention (CDC) through 1995.[10] The distributions by age, sex, race, and risk groups were similar to those reported to the CDC.[10] Therefore, our study population closely reflected the profile of pediatric AIDS cases in the United States.

Most cancers occurring in children with AIDS were NHL, but excesses of KS, Hodgkin disease, and leiomyosarcoma were significant. Overall, 2.5% of children with AIDS developed cancer, which is lower than the proportion seen in adult AIDS patients.[1,2] Cancer incidence was higher in boys than girls ($P = .04$) and higher in whites ($P = .06$) and Hispanics ($P = .01$) than in blacks, largely because most cancers were NHL. In a prior study, we found similar demographic patterns for NHL in adults with and without AIDS.[1] The only other population-based examination of cancer risk in children with AIDS compared European and US data for NHL and KS at AIDS onset, using proportional rather than incidence-based analysis techniques.[5] Investigators with that study noted a higher proportion of NHL cases in boys, whites, and older children.

In our study, NHLs occurred more frequently and leiomyosarcomas less frequently than in case series reports, which may be biased toward presenting unusual cases. Among NHLs, BL was the most common histological subtype, as previously reported in children.[1,11] However, IBL cases were also frequent, although we note that for 10 of 19 cases, the diagnosis came only from the AIDS rather than the cancer registry. Hence, if some of these IBL diagnoses not confirmed by cancer registry evaluation were really BL, a higher proportion of NHLs may be BL than we credited.

About a quarter of the lymphomas were primary brain lymphomas. Among children without HIV infection, primary brain lymphomas are rare. The relatively high frequency of primary brain lymphoma late in the course of AIDS suggests a high incidence in children with prolonged or profound immunosuppression. Typically, primary brain lymphomas in persons with AIDS have high or intermediate grade histologies,[12,13] but in this study histologies were usually not recorded for primary brain lymphomas.

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The profile of leiomyosarcomas also showed a higher frequency in the late follow-up period, again suggesting a strong role for prolonged or advanced immunosuppression. Proportionately, leiomyosarcomas constituted 3% of all cancers, which was considerably lower than the 17% reported in the largest case series, which included both leiomyosarcomas and leiomyomas.[4] Cancer registries do not collect data on benign soft tissue sarcoma. Referral bias in case series may also contribute to this proportional difference.

The etiology of KS probably involves infection with human herpesvirus 8, a virus with a high prevalence in homosexual and bisexual men.[14] Children infected via transmission from mothers who were in turn infected by a bisexual man are thought to be at increased risk of KS,[15] but only 1 of 8 KS cases in this study had such an exposure. None of the children with KS became HIV infected by sexual routes. The excess of Hodgkin disease in the children with AIDS was based on only 1 case occurring in the 2 years following AIDS onset, but it is statistically significant and is concordant with the excess of Hodgkin disease reported in adults with AIDS.[2]

The occurrence of other or unspecified cancers was increased 3.6-fold, but this finding was not statistically significant. There was no increase in the risk of leukemia or cancers at common pediatric sites, such as kidney or brain (other than lymphoma). Ewing sarcoma and rhabdomyosarcoma have been described in children with AIDS[16] but were not seen in this study. Mucosal-associated lymphoid tissue tumors have also been described in children with AIDS,[4] but the cancer registry data were insufficiently detailed for documentation of these tumors.

In summary, NHLs dominate the profile of cancers occurring in children with AIDS, with BL being the most common specific type. The highest RR was for primary brain lymphoma, and a high proportion of these cancers occurred several years after AIDS onset when subjects were likely to have had prolonged or profound immunosuppression. Leiomyosarcomas also had a late onset pattern. Kaposi sarcoma and Hodgkin disease risks were also increased. The risks of other pediatric cancers were not increased. Thus, AIDS-related immunosuppression does not result in an increase in risk for all cancers in children. Rather, as in adults, the increased risk is limited to a few types that also occur excessively in adults with AIDS, as well as leiomyosarcoma. If children with AIDS survive longer with better therapies, both the risks of cancer and the profile of types could change.

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